

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5: A61K 9/48		A1	(11) International Publication Number: WO 95/00123
			(43) International Publication Date: 5 January 1995 (05.01.95)
(21) International Application Number: PCT/GB94/01361		(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 23 June 1994 (23.06.94)		Published With international search report.	
(30) Priority Data: 9313329.6 28 June 1993 (28.06.93) GB			
(71) Applicant (for all designated States except US): R.P. SCHERER CORPORATION [US/US]; 2075 West Big Beaver Road, Troy, MI 48007-7060 (US).			
(72) Inventors; and (73) Inventors/Applicants (for US only): HUTCHISON, Keith, Graceme [GB/GB]; 8 Cooneygar Road, Quenington, Gloucestershire GL7 5BY (GB). GARNETT, Kelvin, Royce [GB/GB]; 6 Pleydells, Cricklade, Wiltshire SN6 6NG (GB). FISCHER, Gerhard [DE/DE]; Hobenstaufenstrasse 28/1, D-69412 Eberbach (DE). PAGE, Nicola, Sandra [GB/GB]; Ashtree Cottage, Highworth Road, South Marston, Wiltshire (GB).			
(74) Agent: HITCHCOCK, Esmond, Antony; Lloyd Wise, Tregear & Co., Norman House, 105-109 Strand, London WC2R 0AE (GB).			
(54) Title: SOFT GELATIN CAPSULE SHELL COMPOSITIONS			
(57) Abstract A composition for use in the shell of a comestible capsule comprising Gelatin and a plasticiser such as Glycerol together with a further component which forms a secondary matrix for the plasticiser. The provision of this secondary matrix enables the relative amount of the gelatin to the plasticiser to be reduced which shortens disintegration time in the mouth. The further component is typically unbleached potato starch acetate.			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Ghana	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LJ	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

SOFT GELATIN CAPSULE SHELL COMPOSITIONS

This invention relates to compositions for the use in comestible and other soft gelatin capsules, of the type used in oral drug delivery systems and in food products and food additives.

5 It is known to encapsulate medicinal and food products using capsule material which is itself comestible. The shell material for such capsules is normally gelatin based, and as a consequence largely void of flavour, odour and colour. While such capsules
10 have been used with great success, gelatin based shell materials can be relatively slow in disintegrating, and particularly where an encapsulated product for oral use is intended to be released in the mouth, faster disintegration rates are desirable.

15 Examples of gelatin based capsules are described in the following Patent Specifications to which reference is directed:

EP -A- 0 233 231 & US -A- 4,804,542

EP-A- 0 199 034

20 EP -A- 0 120 248 & US -A- 4,744,988

US-A- 2 580 863

Shell materials of the above type normally comprise Gelatin and a physiologically acceptable plasticiser such as Glycerol, the Gelatin forming a matrix for the
25 plasticiser. The relative quantities of these components is important to ensure reliable encapsulation, and storage characteristics. However, we have found that the amount of Gelatin can be reduced if a further component is included which forms a secondary
30 matrix for the plasticiser. According to the invention therefore, a composition for use in the shell of a capsule comprises Gelatin and a plasticiser, the Gelatin forming a primary matrix for the plasticiser; and a further component compatible with the Gelatin, which
35 component forms a secondary matrix for the plasticiser.

Typically, the composition includes 18 to 30% by weight of Gelatin and 30 to 45% by weight of the plasticiser. The further component is normally a potato starch acetate, another starch derivative, starch itself or mixtures thereof.

The invention also provides chewable compositions formulated according to the above criteria, and comestible capsules with shells comprising such compositions. Additionally disclosed herein is a process for the preparation of a composition according to the invention comprising the steps of mixing the further component with water and the plasticiser; adding the gelatin to the mixture; allowing the mixture to crumb; heating the mixture; leaving the heated mass to stand; and deaerating the mass with minimum water loss.

In preferred compositions according to the invention the amount of the further component does not exceed 25%, and is normally no more than 12% by weight. The preferred further component is unbleached starch acetate, most preferably derived from potato, and a suitable product is available under the Trade Name PERFECTAMYL GEL MB from Avebe BA. Another suitable potato starch acetate is available from Roquette Freres, under the Trade Name CLEARAM.

A typical amount of the further component is up to 12% by weight. While higher levels result in a more chewable product, solubility is likely to deteriorate. Additionally, examination of capsules formed from selected compositions using higher levels of starch acetate as the further component, showed that some starch aggregation was taking place. A preferred maximum level is 10%; 8% is particularly preferred.

The quantities of gelatin specified above are substantially less than is normally used in known gelatin based capsule shell compositions. Similarly, the amount of plasticiser is relatively increased. This

is made possible by the presence of the further component which reduces the effect of the plasticiser on the gelatin which might otherwise result in a composition which does not form a structure of strength sufficient for encapsulation and storage. In effect, the further component forms a secondary compatible matrix, typically in the range 20° to 60°C, for the plasticiser within the primary gelatin matrix which does not adversely effect the function of the plasticiser, but reduces its tendency to form an adherent surface on the eventual product. It will be appreciated that a certain quantity of the further component is always required in the composition, and a typical minimum level would be 3% by weight.

The plasticiser is usually Glycerol, but suitable alternatives are Xylitol, Sorbitol, Polyglycerol, non-crystallising solutions of Sorbitol, glucose, fructose and glucose syrups with different equivalents. One preferred alternative is ANIDRISORB (a proprietary mixture of Sorbitol, Sorbitans, Maltitol and Mannitol, available from Roquette Freres). These may be used alone or in combination. In a combination of plasticisers including Glycerol, the Glycerol typically comprises at least 30% by weight of the combination, normally in the range 30% to 70% by weight. The inclusion of Glycerol provides a more 'chewable' product. Using an alternative plasticiser or plasticiser component produces a less 'chewable' product, but one which does disintegrate more quickly than known formulations.

The chewability of compositions according to the invention can be enhanced by the inclusion of an oil such as fractionated coconut oil. Up to 15%, preferably no more than 10%, can be included in the composition, but at high levels, the resultant product appears cloudy. A preferred quantity is around 3% to 7%, typically 5% by weight. Oil disperses within the shell

structure as microscopic droplets. These prevent some of the gelatin bonds forming, and hence act in a similar way to the plasticiser. However, the plasticiser can allow a formation of hydrogen bonds across the
5 interstitial spaces of the gel matrix and some of the liquid in the spaces is removed as the gel dries. As a result more gelatin links form, stiffening the matrix. The oil inhibits the formation of these additional gelatin links resulting in a more chewable product,
10 although the pressure exerted by the gelatin causes some droplets to coalesce.

Preferred embodiments of the invention also include a bleached starch acetate, normally derived from potato, and typically in an amount up to 12% by weight,
15 preferably 6% to 10%. A suitable such potato starch derivative is also available from Avebe BA under the Trade Name PERFECTAMYL GEL 45. This starch derivative is soluble in the manufacture of compositions according to the invention, and therefore remains in solution
20 until the composition dries. At this stage the bleached starch acetate forms a film, thus acting as a bulking agent. It causes a degree of stickiness in the composition as it sets, which is counteracted by the setting of the gelatin and the preferred further
25 component; unbleached starch acetate. A combination of both starches was found to replace higher levels of gelatin than the unbleached acetate alone. Similar effects can be achieved by using a variety of soluble materials.

30 Capsules may be formed using compositions according to the invention by any suitable technique. Two such techniques are the concentric cylinder and the rotary dye methods. The latter has been used for many years by R.P. Scherer Corporation and its associated companies,
35 and is described in the September 1985 edition of Pharmaceutical Technology, to which reference is directed. Briefly, the composition in a liquid state is

spread on a suitably prepared and cooled drum upon which the gel mass sets to a non-sticky film. Where two similar films merge on encapsulation, seals are formed which become stronger as the mass dries. The further component makes a significant contribution to film strength at this stage, and in this respect its selection is important. The preferred component is potato starch acetate which adds structure to the gel matrix by the association of starch molecules to form a starch gel inside the gelatin matrix.

The use of bleached starch in addition to the unbleached starch results in improved suitability for chewing because the starches swell at a different rate to gelatin without substantial cross-bonding. Consequently, they are readily separable on chewing.

Compositions embodying the invention and a known composition, will now be described by way of example. Details of the compositions are as follows.

Formulations used in which the plasticiser is Glycerol

Material	Formulation Number					
	1	2	3	4	5	6
% by weight						
Gelatin	26	26	24	28	26	38.4
Glycerol	35	35	40	39	36	29.2
Water	27	22	20	25	22	32.4
Potato Starch Acetate	12	10	6	3	6	-
Bleached Potato Starch Acetate	-	7	10	-	10	-
Oil	-	-	-	5	-	-

Example S1 (using formulation 1)

A gelatin decoction was prepared by blending the Potato Starch Acetate with the water and glycerol to form a slurry. After addition of the gelatin with stirring, and allowing the mixture to 'crumb' under vacuum for ten minutes, the decoction was prepared in a

per se known manner using a waterbath with circulator in which to heat the vessel containing the mixture to 90°C and leaving to stand for 35 minutes. The gel mass is then deaerated using a vacuum pump while minimising water loss.

Capsules were readily made with a flavoured placebo paste formulation for fill, which were easily chewable.

Example S2 (using formulation 2)

A gelatin decoction was prepared by blending both starch derivatives with the water and glycerol to form a slurry. After addition of the gelatin, the decoction was prepared in a per se known manner.

Capsules were readily made with a flavoured placebo paste formulation for fill, which were very easily chewable.

Example S3 (using formulation 3)

A gelatin decoction was prepared as described in example S2. To this was added colours and flavours totalling 6.0% of the gelatin mass using a high speed blender.

Capsules were readily made with a flavoured placebo formulation for fill. These capsules were very easily chewable.

Example S4 (using formulation 3)

The gelatin decoction described was blended to colour and flavour and used to make capsules with an oil fill material. Disintegration testing in distilled water at 70°C gave results of capsule rupture and full shell disintegration approximately 40-50% faster for the capsules using the invention than the known shell formulation (6).

Example S5 (using formulation 4)

A gelatin decoction was prepared as described in

example S2 with the component of formulation 4 excluding the oil. To this decoction was added colours and flavours identical to example S3 and vegetable oil 3% (flavour oil level was 2% making a total oil content of 5%).

Capsules were readily made with a flavoured placebo paste fill which were soft and easily chewable.

Examples S6, S7 and S8 (using formulation 5)

Gelatin decoctions were prepared as described in example S2.

These were blended to different colours and flavours with a range of additions of 3-7.2% of the gelatin decoction used.

Capsules with flavoured paste fills containing active vitamin compositions were readily made. All were easily chewable with a very notable improvement compared to the same recipes using formulation 6 as the base shell formulation.

Example S9 (using formulation 5)

A gelatin decoction was prepared in two stages. First, the Potato Starch derivatives were blended with 1½ times their own weight of glycerol from the formulation. This slurry was heated to 50-60°C and added to a gelatin decoction made from all remaining materials in a per se known manner. The mixture was stirred on a high speed blender until a temperature of 60-65°C was attained. This mixture was then further blended with colours and flavours totalling 6.25% of the mixture weight.

Capsules with flavoured paste fill containing active vitamin components were readily made and were identical in chewability to the same formulation of capsules made in Example S7.

Example S10 (prior art, using formulation 6)

A standard shell was prepared in a per se known manner and blended to the same colour and flavour and used to make capsules with the same fill formulation. These capsules had a very tough chewing characteristic requiring approximately twice the time (60-65 secs) to chew before swallowing. A slippery, slimy mouth feel was also noted for these capsules.

Formulations used including alternative plasticisers

Material	Formulation Number				
	7	8	9	10	11
% by weight					
Gelatin 195 Bloom Acid processed	25		25	25	25
Gelatin Succinated		34			
Glycerol	24	20	24	12	
Sorbitol 70%	12	10		24	
Anidrisorb 85/70			12		
Polyglycerol					36
Purified Water	23	29	23	23	
Potato Starch Acetate	6	3	6	6	6
Bleached Potato Starch Acetate	10	4	10	10	10

Examples S11 to S14

Gelatin decoctions were prepared using formulations 7 to 11, by first blending the starch derivatives with the water and plasticiser components (Glycerol, Sorbitol, Andrisorb, Polyglycerol) to form a slurry, to which the Gelatin was added as in Example S2. Capsules made according to these examples exhibit short disintegration times on contact with water, but are less readily chewable than those made according to Examples S1 to S9.

From experimental work conducted using the above examples it appears that any plasticiser normally used in soft gelatin capsules can be used in compositions embodying this invention. The matrix formed by the lower Gelatin content, modified starch components, and high plasticiser content give faster disintegration times than those exhibited by known formulations, although improvement in chewability was clearly most apparent in the formulations which used Glycerol as the plasticiser and/or an oil.

As will be apparent from Examples S1 to S10 above, the material in capsules of the present invention of the wall can itself contain significant components contributing to its overall properties. This is of particular value where two component elements are to be kept separate prior to use and they may, of course, be kept separate between the capsule material and the encapsulated product.

Products provided in liquid form for encapsulation in capsules of the invention typically incorporate hydrophobic or hydrophilic carrier media or a combination of both. Examples of hydrophilic solvents or carrier media include: Polyethylene Glycols (PEGs), particularly PEG 400 and PEG 600; Glycofurol; Polyglycerols; propylene Glycol; Ethanol; Water; Glycerol; transcitol, polysorbate and propylene carbonate.

Hydrophobic solvent/carrier media also include hydrogenated natural oils, synthetic oils such as polymethylsiloxane (dimethicone), neutral oils such as fractionated coconut oil, mineral oils, triacetin, ethyl oleate, and other natural oils such as: Soyabean Oil; Arachis Oil; Corn Oil; Sesame Oil; Olive Oil; Rapeseed Oil; Sunflower Oil and Safflower Oil. Thickened fill products with high viscosities are preferred as they disperse less rapidly and improve palatability. They also reduce the contrast between the shell and the fill

materials.

Capsules embodying the invention can include flavouring and aromatic components, in either the encapsulated contents, or in the capsule shell material itself. Suitable components include essential oils such as lemon, orange and peppermint oils; fruit flavours; aniseed; liquorice; caramel; honey; cream; various spices and combinations of these and other flavours. Such components are available from International Flavours & Fragrances, IFF (GB) Ltd. of Haverhill, Suffolk, CB9 8LG ENGLAND. Natural or artificial sweeteners can also be used, such as:

Aspartame, Saccharin, Acesulphame K, Neohesperidine hydrochloride, Mannitol, Xylitol, and Maltitol;

-taste-masking ingredients such as sodium bicarbonate, ion exchange resins, cyclodextrins and adsorbates;

-suspending agents such as beeswax, hydrogenated vegetable oils, glycerol monostearate or glycerol palmitate, and high molecular weight PEGs; e.g. 1500 to 6000.

Where the encapsulated contents include particles in suspension, the particles may be separately coated, typically with suitably sweetened or flavoured coatings, such as those referred to above. Such a coating can serve as either or both of a taste-masking agent and a stabiliser in the suspension.

30

By way of further illustration some contents formulations will be given by way of example.

35

Example C1

Fractionated Coconut Oil BP/PhEur	75%
Gelucire 42/12 *	7%
Span 20 **	3%

11

	Mannitol BP	9%
	Aspartame US NF XVII	1%
	Flavour	5%
5		<hr/> 100%
	* Glycerides and polyglycides of fatty acids of vegetable origin.	
10	** Sorbitan fatty acid esters (BP 1980)	
	<u>Example C2</u>	
	Imwitor 742 *	80%
	Tween 80 **	14%
15	Aspartame US NF XVII	1%
	Flavour	5%
		<hr/> 100%
20	* Caprylic/Capric mono-di & tri-glycerides (Medium chain partial glycerides US NF XVII)	
	** Polysorbate 80 BP	
	<u>Example C3</u>	
25	Polyethylene Glycol 400 BP	56%
	Glycerol BP	8%
	Water, Purified BP	5%
	Mannitol BP	25%
30	Aspartame US NF XVII	1%
	Flavour	5%
		<hr/> 100%
35	<u>Example C4</u>	
	Lycasin 80/55 *	88.5%
	Aerosil 200 **	1.5%
	Glycerol BP	5%
40	Flavour	5%
		<hr/> 100%
45	* Hydrogenated Glucose Syrup	
	** Colloidal Silicon Dioxide	
50	<u>Example C5</u>	
	Fractionated Coconut Oil BP	58%
	Tween 80 *	25%
	Mannitol BP	10%
55	Sodium Saccharin BP	2%
	Flavour	5%

			<u>100%</u>
5	* Polysorbate 80 BP		
	<u>Example C6</u>		
10	Fractionated Coconut Oil BP	95%	
	Flavour	5%	
		<u>100%</u>	
15	<u>Example C7</u>		
	Fractionated Coconut Oil BP/Ph Eur	75%	
	Gelucire 42/12	7%	
	Span 20	3%	
20	Mannitol BP	9%	
	Peppermint Oil BP	6%	
		<u>100%</u>	
25	<u>Example C8</u>		
	Fractionated Coconut Oil BP/Ph Eur	75%	
	Gelucire 42/12	7%	
30	Span 20	3%	
	Mannitol BP	9%	
	Aspartame US NF XVII	1%	
	Peppermint Oil BP	5%	
35		<u>100%</u>	
	<u>Example C9</u>		
40	Polyethylene Glycol 400 BP	53.3%	
	Glycerol BP	7.6%	
	Water Purified BP	4.8%	
	Paracetamol BP	28.6%	
	Aspartame US NF XVII	1.0%	
45	Lemon Flavour 17.42.7201	4.8%	
		<u>100%</u>	
50	<u>Example C10</u>		
	Polyethylene Glycol 400 BP	53.3%	
	Glycerol BP	7.6%	
55	Water Purified BP	4.8%	
	Paracetamol BP	28.6%	
	Saccharin, Sodium BP	1.0%	

WO 95/00123

PCT/GB94/01361

13

Lemon Flavour 17.42.7201

4.8%

100%

5

CLAIMS

1. A composition for use in the shell of a capsule comprising Gelatin and a plasticiser, the Gelatin forming a primary matrix for the plasticiser; and a further component compatible with the Gelatin, which component forms a secondary matrix for the plasticiser.
2. A composition according to Claim 1 including 18 to 30% by weight of Gelatin and 30 to 45% by weight of the plasticiser.
3. A composition according to Claim 1 or Claim 2 wherein the plasticiser is selected from Glycerol, Xylitol, Sorbitol, Polyglycerol, non-crystallising solutions of Sorbitol, glucose, fructose, glucose syrup, and combinations thereof.
4. A composition according to Claim 3 wherein the plasticiser is Glycerol.
5. A composition according to any preceding Claim wherein the further component is starch, a starch derivative, or a mixture thereof.
6. A composition according to Claim 5 wherein the further component is unbleached starch acetate.
7. A composition according to Claim 6 wherein the unbleached starch acetate is unbleached potato starch acetate.
8. A composition according to any preceding Claim including up to 12% by weight of the further component.
9. A composition according to Claim 8 wherein the amount of the further component is in the range 3 to 10% by weight.
10. A composition according to any preceding Claim including up to 10% by weight of oil.
11. A composition according to Claim 10 wherein the oil is fractionated coconut oil.
12. A composition according to any of Claims 1 to 9 including up to 12% bleached starch acetate.

13. A composition according to Claim 12 wherein the bleached starch acetate is derived from potato.

5 14. A chewable composition according to any preceding Claim.

15. A comestible capsule with a shell comprising a composition according to any preceding Claim.

10 16. A process for the preparation of a composition according to any of Claims 1 to 14 comprising the steps of mixing the further component with water and the plasticiser; adding the gelatin to the mixture; allowing the mixture to crumb; heating the mixture; leaving the heated mass to stand; and deaerating the mass with minimum water loss.

15 17. A process according to Claim 16 wherein the further component is unbleached starch acetate.

INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/GB 94/01361

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,92 09274 (SCHERER CORPORATION) 11 June 1992	1-5,8,9
Y	see claims 1,2	6,7,12, 13
X	EP,A,0 326 517 (WARNER-LAMBERT COMPANY) 2 August 1989 see claims 1,7-9,13,18 see column 6, line 21 - line 27	1,3-5, 8-10
X	US,A,4 428 927 (WILLIAM R. EBERT, ET AL.) 31 January 1984	1,3,4,8, 9,14-16 17
Y	see claim 1 see column 1, line 14 - line 19 see column 2, line 21 - line 24 see column 3, line 28 - line 35	
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *B* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

A document member of the same patent family

Date of the actual completion of the international search

7 September 1994

Date of mailing of the international search report

20.09.94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Ventura Amat, A

INTERNATIONAL SEARCH REPORT

Intern U Application No
PCT/GB 94/01361

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DD,A,272 999 (MARTIN-LUTHER-UNIVERSITÄT HALLE) 1 November 1989 see claims 1-6 -----	6,7,12, 13,17

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat'l Application No

PCT/GB 94/01361

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9209274	11-06-92	AU-A- 9145691 EP-A- 0559827	25-06-92 15-09-93
EP-A-0326517	02-08-89	GB-A- 2214516 AT-T- 108189 AU-A- 2858989 DE-D- 68916556 JP-A- 1217002 SU-A- 1743357	06-09-89 15-07-94 27-07-89 11-08-94 30-08-89 23-06-92
US-A-4428927	31-01-84	US-A- 4532126 AU-B- 559817 AU-A- 2238483 CA-A- 1209039 DE-A- 3347386 FR-A,B 2557429 GB-A,B 2151201 JP-A- 60139617	30-07-85 19-03-87 20-06-85 05-08-86 11-07-85 05-07-85 17-07-85 24-07-85
DD-A-272999		NONE	